

# PATENT SPECIFICATION

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(19)



## (54) AN APPARATUS FOR CONTROLLING A QUANTITY OF INSULIN INFUSION

(71) We, NIKKISO COMPANY LIMITED, a Japanese company of No. 43-2, 3-chome, Ebisu, Shibuya-ku, Tokyo, Japan do hereby declare the invention for which we pray that a patent may be granted to us and the method by which it is to be performed to be particularly described in and by the following statement:-

This invention relates to an improved artificial beta cell for controlling a quantity of insulin infusion, especially to normalize blood glucose concentrations of diabetics on a minute-by-minute basis.

The discovery of insulin in 1921 allowed the successful treatment of the acute manifestations of diabetes. But the replacement therapy by intermediate-acting insulin injection once a day for diabetics was revealed to be ineffective to normalize the blood glucose concentration, especially in the post-prandial period. Thus, high glucose levels of diabetics seem to result in the onset or progress of the chronic complications.

Recently with introduction of the computer, new techniques for elaborating the measurement, communication and operation to achieve the adaptive control have been developed in some fields of medicine.

The artificial endocrine pancreas which infuses insulin and glucose in relation to the blood concentrations measured by rapid chemical determinations on continuous blood sampling has been developed and reported from a few institutes (Albisser et al. 1974a, b; Pfeiffer et al. 1974; Kerner et al. 1976). In these systems, when blood glucose levels were going down to the levels of around 120 mg/100 ml, the rate of insulin infusion was 600 mU/min in 81 kg man (Albisser et al. 1974b). By our calculation, this is equivalent to  $33 \times B$  (hereinafter defined), so peripheral plasma insulin concentration would be 300  $\mu$ U/ml, higher than the upper limits of physiological ranges. In another paper (Kerner et al. 1976), following the 100 g glucose oral administration, the rate of insulin infusion was between 400 and 600 mU/min. In both cases, those high rates of insulin infusion resulted in hypoglycemia which made it necessary to infuse glucose.

To make up computer algorithm of our artificial beta cell, we tried to simulate the insulin response in the blood glucose regulatory system. With the aid of proportional and derivative mode of control, we would simulate the glucose-induced insulin secretion.

Two important characteristics reside in our artificial beta cell, the first is that because insulin is infused in a proportional plus derivative action to blood glucose concentration, so the rate of insulin infusion is small enough to keep the plasma concentration of insulin physiological; thus insulin requirements are reduced to around a half of those given subcutaneously. The second is that glucose or glucagon infusion to restore hypoglycemia is not necessarily needed.

As a result of study in the effect of insulin on the rate of change in glucose concentration (i.e. derivative action) in glucose tolerance, it has been found that when the derivative action was added to the proportional action properly in insulin infusion regulatory system, the insulin requirement was the smallest and glucose regulation was the best among experimental groups. It has been also found that when insulin infusion was based only on the blood glucose concentration, it could not regulate the glucose assimilation curves following intravenous glucose challenge and what is worse, late hypoglycemia occurred. In this specification, the term "proportional action" means that insulin secretion responds to the glucose concentration per se, whereas the term "derivative action" means that the insulin secretion responds to the rate of change in glucose concentration.

Therefore, a principal object of the invention is to provide an artificial beta cell for controlling a quantity of insulin infusion comprising a glucose-sensor for continuously measuring blood glucose concentration, a computing circuit for calculating a quantity of insulin infusion corresponding to the measured blood glucose concentration, an infusing means of insulin and a printer for registering the time, the measured blood glucose, forecasted blood glucose and insulin infusion rate every minute, in which a real quantity of insulin required is calculated in the computing circuit based on the blood glucose concentration and the rate of change in blood glucose concentration depending on an individual basis.

In the apparatus according to the invention, the real quantity of insulin required is computed in the computing circuit in accordance with the following equation:

$$I.I.A. = \theta(K \cdot D \times a \times \overline{BS} + (a + b \times K \cdot D) \Delta \overline{BS} + c \times K \cdot D) \dots (1)$$

wherein I.I.A. is insulin infusion rate ( $\mu U/\text{min}$ ),  $\theta$  is insulin space [ $\text{body weight} \times \frac{10^7}{(\text{ml})}$ ],  $D$  is insulin degradation rate ( $\text{min}^{-1}$ ),  $K$  is diffusion constant (dimensionless),  $\overline{BS}$  is blood glucose concentration ( $\text{mg}/100\text{ml}$ ),  $\Delta \overline{BS}$  is rate of change in blood glucose concentration ( $\text{mg}/100\text{ml} \cdot \text{min}$ ) and  $a$ ,  $b$  and  $c$  are intrinsic constants for an individual (for example patient), i.e.

$$\begin{aligned} a &: 100 \mu U/\text{mg} \\ b &: 100 \mu U \cdot \text{min}/\text{mg} \\ c &: \mu U/\text{ml} \end{aligned}$$

The equation (1) could be obtained by the following assumptions. Namely, plasma insulin concentration  $\overline{IRI}$  may be represented with two independent variables, i.e. the one is the blood glucose concentration  $\overline{BS}$  ( $\text{mg}/100\text{ml}$ ), the other is the rate of change in blood glucose concentration  $\Delta \overline{BS}$  ( $\text{mg}/100\text{ml} \cdot \text{min}$ ), as follows:

$$\overline{IRI} = a \times \overline{BS} + b \times \Delta \overline{BS} + c \dots (2)$$

wherein  $a$ ,  $b$  and  $c$  are intrinsic constants for an individual. Next, the exogenously administered insulin is distributed into the insulin space and degraded by the liver and other organs, then diffused uniformly to reflect the insulin concentration in peripheral vein. This phenomenon was expressed in the following:

$$\frac{d(\theta \cdot \overline{IRI})}{dt} = I.I.A. - K \cdot \theta \cdot \overline{IRI} \cdot D \dots (3)$$

wherein  $\overline{IRI}$  is plasma insulin concentration in peripheral vein ( $\mu U/\text{ml}$ ),  $I.I.A.$  is insulin infusion rate ( $\mu U/\text{min}$ ),  $\theta$  is the insulin space ( $\text{g}$ ),  $D$  is insulin degradation rate ( $\text{min}^{-1}$ ), and  $K$  is diffusion constant (dimensionless). As the  $\overline{IRI}$  is difficult to be analyzed within a short time, this factor  $\overline{IRI}$  is eliminated from the equations (2) and (3), resulting in the above-described equation (1).

In the equation (1) according to the invention, the maximum quantity of insulin infusion is preferably established at the quantity 30 times as much as that of the basal insulin infusion necessary for normal metabolism of glucose.

Other objects and advantages of the invention will become obvious after considering the discussion of the invention in connection with the preferred embodiments thereof shown in the accompanying drawings in which:

Figure 1 is a systematic view of the artificial beta cell according to the present invention; Figures 2 to 5 are graphic curves showing glucose assimilation curve and insulin infusion pattern.

Figure 1 shows a fundamental structure of the apparatus according to the invention, in which the blood glucose concentration is determined by a glucose-sensor 12 for a diabetic 10 which has malfunction in secretion of insulin. A signal of blood glucose concentration thus determined by the glucose sensor 12 is transmitted to a computer 16 which has a predetermined program for calculating a proper quantity of insulin infusion to the diabetic and controls a pump 18 for injecting the corresponding quantity of insulin from a storing vessel 20 of insulin to the diabetic 10. A printer 14 is provided for registering the time, the measured blood glucose, forecasted blood glucose and insulin infusion rate every minute.

In the apparatus according to the invention, the computing circuit 16 calculates the proper quantity of insulin infusion in accordance with the following equation:

$$I.I.A. = \theta(K \cdot D \times a \times \overline{BS} + (a + b \times K \cdot D) \Delta \overline{BS} + c \times K \cdot D) \text{ in which } I.I.A. \text{ is insulin}$$

infusion rate ( $\mu\text{U}/\text{min.}$ ),  $\theta$  is insulin space ( $\text{body weight} \times \frac{10^{-7}}{100} (\text{ml})$ ),  $D$  is insulin degradation rate ( $\text{min}^{-1}$ ),  $K$  is diffusion constant (dimensionless),  $BS$  is blood glucose concentration ( $\text{mg}/100 \text{ ml}$ ),  $\Delta BS$  is rate of change in blood glucose concentration ( $\text{mg}/100\text{ml}.\text{min.}$ ), and  $a$ ,  $b$  and  $c$  are intrinsic constants for an individual, i.e.

$$\begin{aligned} a &: 100 \mu\text{U}/\text{mg} \\ b &: 100 \mu\text{U}.\text{min}/\text{mg} \\ c &: \mu\text{U}/\text{ml} \end{aligned}$$

In order to determine the suitable values for  $a$ ,  $b$  and  $c$  in the equation (1), glucose solution was administered as intravenous glucose pulse loads to normal dogs, and data were obtained when  $\Delta BS$  was below zero and then  $\Delta BS$  was above zero during which time  $20\text{mg}/\text{Kg}.\text{min.}$  of glucose was administered persistently for 60 minutes. The data thus obtained were analyzed with the aid of multiple regression analysis to obtain the following values:

$$\Delta BS > 0 : a = 0.137, b = 4.10, c = -1.95$$

$$\Delta BS < 0 : a = 0.088, b = -1.29, c = 2.20$$

The insulin space  $\theta$  is determined by the method of Sherwin et al and found to be  $0.167 \times \text{body weight (g)}$ .

The insulin degradation rate  $D$  is determined by the method of Stimler and found to be  $0.148 \text{ min}^{-1}$ .

The diffusion constant  $K$  (dimensionless) is determined by utilizing a depancreatized dog and analyzing the relationship between a quantity of insulin infusion and an insulin level in peripheral vein, and found to be 1.46. However, it has been confirmed that the clinically suitable value of  $K$  is 1.2.

In the following, the examples according to the present invention are illustrated.

#### EXAMPLE 1

##### (Intravenous glucose pulse loads test)

Glucose was injected into a jugular vein of a depancreatized dog in an amount of  $0.33 \text{ g}$  glucose per  $\text{Kg}$  of body weight in 10 seconds, and thereafter blood glucose concentration is determined over a period of 80 minutes. After discontinuation of insulin infusion to the dog for more than 24 hours and with fasting for 16 hours,  $5000 \mu\text{U}/\text{Kg}.\text{min.}$  of insulin was persistently injected into peripheral vein. When the blood glucose level was reduced to  $120\text{mg}/100\text{ml}$ , the quantity of insulin injection was reduced to  $225 \mu\text{U}/\text{Kg}.\text{min.}$  (herein, this quantity is referred to as  $B$ , representing the basal insulin infusion). Then, it has been observed that when finishing the insulin injection after the intravenous glucose pulse loads the blood glucose concentration was reduced to  $170 \text{ mg}/100\text{ml}$  over a period of 40 to 60 minutes but thereafter started to increase again.

Under the similar condition, insulin was injected to the depancreatized dog in an amount of  $100 \times B$  for the first one minute, which amount corresponds to the insulin level in portal blood which had been obtained by applying the glucose loads test to normal dogs, and thereafter injected persistently in an amount of  $10 \times B$ . In this case, it has been observed that the glucose assimilation curve is slightly delayed in contrast to that of a normal dog and that the utilization constant of glucose ( $K$  value) was normal ( $3.1 \pm 0.3$ ). However, when the insulin injection was maintained in the amount of  $10 \times B$ , hypoglycemia was observed after 80 minutes (Figures 2a and 2b).

Based on the above observation, insulin was injected according to the predetermined program in such a manner that the maximum insulin infusion was set to the quantity of  $30 \times B$ . The results are shown in Figures 3a and 3b. The Figures show that the blood glucose concentration per se and the rate of change in blood glucose concentration became higher for the first one minute due to the rapid and large dose of glucose. According to the calculation from the equation (1), a quantity of  $177 \times B$  of insulin was needed, but actually  $30 \times B$  of insulin was injected based on the programming. As a result, only  $3 \times B$  of insulin was sufficient thereafter to regulate the blood glucose level in the similar pattern as in Figure 2a (see, Figure 3a). Further, 80 minutes later the quantity of insulin required was reduced to  $B$ , but the blood glucose level could be maintained in the normal range without causing hypoglycemia. Thus, by employing the programming dosage, total insulin consumption could be reduced to 50% or less of that required in Figure 2b (see, Figure 3).

**EXAMPLE 2***(Oral glucose loads test)*

While insulin was orally administered to the depancreatized dog in an amount of B to maintain the normal blood glucose level, 2.0g per Kg body weight of glucose was administered. While continuously administering insulin in an amount of B, the change in blood glucose concentration was determined for 3 hours. The results are shown in Figure 4 a and 4 b. On the other hand, insulin was administered according to the predetermined program as described in Example 1, about  $3 \times B$  of insulin could regulate the blood glucose in the normal range over the period of 4 hours (see, Figures 5 a and 5 b).

**EXAMPLE 3***(Medical test for diabetic coma)*

Hitherto, it has been a principle to administer a large dosage of insulin for the medical treatment of diabetic coma and diabetic ketoacidosis.

Discontinuation of insulin treatment for 3 to 9 days caused serious diabetic ketoacidosis in the depancreatized dog. Then, an insulin solution in an amount of  $5 \times B$  to  $100 \times B$  was injected to the dog persistently for at least 3 hours. The insulin solution had been prepared by adding insulin Actrapid to a physiological saline solution containing 0.5% of gelatine. Determination of the rate of drop in blood glucose revealed that the maximum average rate of drop (121mg/dl/hr.) was achieved by using the quantity of  $30 \times B$  of insulin, and that better results had never been obtained with larger quantity than  $30 \times B$ .

According to the present invention, the quantity of insulin necessary to maintain the blood glucose level in the normal range can be reduced greatly, as well as can be calculated on the individual basis due to the factors a, b, c and  $\theta$  in the above-described equation (1).

While certain preferred embodiments of the invention have been illustrated by way of example in the drawings and particularly described, it will be understood that various modifications may be made in the arrangement and that the invention is no way limited to the embodiments shown.

**WHAT WE CLAIM IS:-**

1. An artificial beta cell for controlling a quantity of insulin infusion comprising a glucose-sensor for continuously measuring blood glucose concentration, a computing circuit for calculating a quantity of insulin infusion corresponding to the measured blood glucose concentration, an infusing means of insulin and a printer for registering the time, the measured blood glucose, forecasted blood glucose and insulin infusion rate every minute, in which a real quantity of insulin required is calculated in the computing circuit based on the blood glucose concentration and the rate of change in blood glucose concentration depending on individual basis.

2. An artificial beta cell as claimed in claim 1 in which a real quantity of insulin required is calculated in accordance with the following equation.

$$I.I.A. = \theta(K \cdot D) \times a \times \overline{BS} + (a + b \times K \cdot D) \cdot \Delta \overline{BS} + c \times K \cdot D$$

wherein I.I.A. is insulin infusion rate (U min.),  $\theta$  is insulin space D is insulin degradation rate (min<sup>-1</sup>), K is diffusion constant (dimensionless),  $\overline{BS}$  is blood glucose concentration (mg 100ml),  $\Delta \overline{BS}$  is rate of change in blood glucose concentration (mg 100ml.min.) and a, b and c are intrinsic constants for an individual, i.e.

a : 100  $\mu$ C mg

b : 100  $\mu$ C.min mg

c :  $\mu$ C ml

3. An artificial beta cell as claimed in claim 2 in which the maximum quantity of insulin infusion is defined at the quantity 30 times as much as that of the basal insulin infusion necessary for normal metabolism of glucose.

4. An artificial beta cell for controlling a quantity of insulin infusion as hereinbefore substantially described with reference to the drawings

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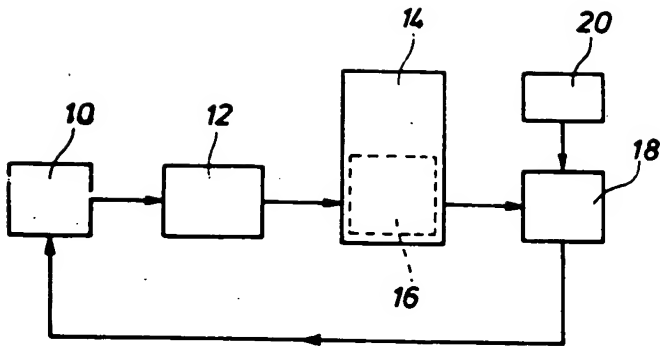
Nottingham.

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COMPLETE SPECIFICATION

3 SHEETS

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Sheet 1*



**FIG. 1**

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Sheet 2

FIG.3a

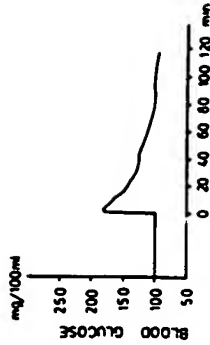


FIG.3b

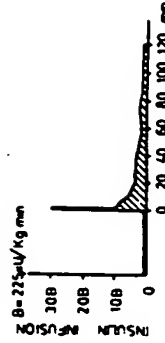


FIG.2a

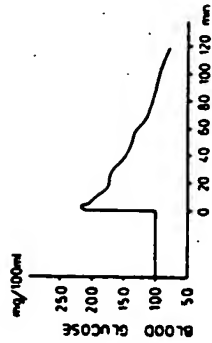
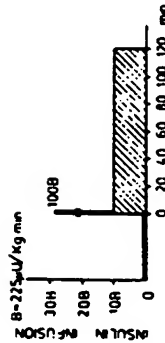


FIG.2b



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FIG.5a

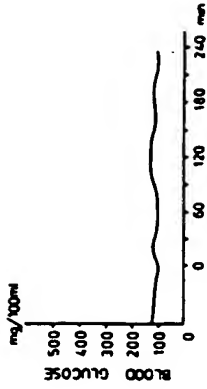


FIG.5b

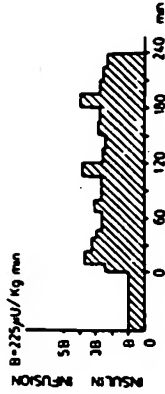


FIG.4a

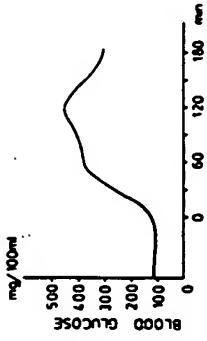


FIG.4b

